application was filed, had possession of the claimed invention was maintained. This rejection is respectfully traversed.

The Examiner maintains that the conditions of 37 C.F.R. 1.801-1.809 remain unmet. Applicants disagree. A Statement of Availability concerning the deposit of hybridoma cell line D7 in accordance with the Budapest Treaty and signed by an attorney of record was submitted on May 30, 2002. In addition, the specification was amended on May 30, 2002, by replacement of the paragraph beginning at page 4, line 6, to recite the date of the deposit and the complete name and address of the depository.

The biological deposit was made after the effective filing date of the application, and the Examiner, citing *In re Lundak*, 773 F. 2d 1216, 227 USPQ 90 (CAFC 1985), notes that a verified statement is required from a person in position to corroborate that the deposited hybridomas are producing the monoclonal antibodies as described in the specification as filed and are the same as those deposited in the depository. In response thereto, Applicants submit the Declaration of Michael Kinch, Ph.D., providing the requested corroborative evidence.

It is respectfully submitted that the requirements of 37 C.F.R. 1.801-1.809 are now satisfied. Reconsideration and withdrawal of the rejection of claims 4, 31, 50 and 54 under 35 U.S.C. §112, first paragraph, is respectfully requested.

The Examiner rejected claims 1, 3, 5-13, 21-24, 28-30, 32-47, 49, 51-53, 55-69, 72, 73, 75-81, 90 and 91 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

The Examiner notes that the pending claims are drawn to methods for detecting metastatic cells which are dependent upon the detection of EphA2, and maintains that the specification is insufficient because it does not define EphA2 in terms of sequence or structure. The Examiner states that "[g]iven the broadest reasonable interpretation EphA2 could read on a

genus of tyrosine kinases which are up regulated in metastatic cells comprising proteins expressed from allelic variants, splice variants which have not been disclosed."

Applicants vigorously disagree, and submit that the Examiner has not met the initial burden of, after a thorough reading and evaluation of the content of the application, presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.

Applicants contend that one of skill in the art would readily recognize that the written description of the invention provides support for the claims. In describing EphA2, the specification states that EphA2 is a "transmembrane receptor tyrosine kinase with a cell-bound ligand" and "[a] member of the Eph family of tyrosine kinases known as Ephrins" (specification at page 2, lines 5-6). The specification further states the EphA2 was cloned a decade ago, and cites Lindberg, R.A. and Hunter, T., "cDNA Cloning and Characterization of Eck, an Epithelial Cell Receptor Protein-tyrosine Kinase in the Eph/elk Family of Protein Kinases," Mol. Cell. Biol. 10 (12), 6316-6324 (1990) (specification at page 2, lines 7-9). The Lindberg et al. publication, which was of record in the present matter in the Information Disclosure Statement submitted February 12, 2001, reports the nucleotide and amino acid sequence of EphA2, at that time referred to as "Eck".

Furthermore, the structure of EphA2 was well-known to the art at the time of the invention. A simple Medline search (attached as Exhibit A) shows 63 papers identified in response to an "EphA2" inquiry, of which 30 were published prior to August, 2000, the month in which the present application was filed.

Finally, the specification describes hybridoma cell lines producing antibodies D7 and B2D6 that bind EphA2 (specification at page 4, lines 6-12). "The D7 antibodies of this invention are highly specific for an intracellular epitope of EphA2" (specification at page 4, lines 24-25). It is well-known that interactions between antibodies and their targets are structurally defined. As noted above and in the Amendment mailed May 30, 2002, these hybridomas have been deposited in accordance with the Budapest Treaty.

Applicants thus contend that the "sequence or structure" of EphA2 is defined in the specification in a manner that provides sufficient support in the context of the invention *as claimed.* Applicants are not claiming EphA2 *per se*, the structure of which was well-known to the art. Rather, Applicants discovered an important relationship between metastatic cancers and EphA2 expression, and as noted by the Examiner are claiming methods that involve, at some point in the method, identification of metastatic cancer cells that express EphA2. The original paper describing EphA2 nucleotide and amino acid sequences was cited in the specification. Antibodies that specifically bind EphA2 are described in the specification and enabled by a Budapest Treaty deposit. EphA2 has been the subject of numerous publications in the scientific literature without recitation of its structure. The reason given by the Examiner for the insufficiency of the specification (i.e., that the term EphA2 could read on a genus of tyrosine kinases that include proteins expressed from "allelic variants" or "splice variants" that have not been disclosed) fails to sustain the Examiner's burden under the Written Description Guidelines. The Examiner has not shown any ambiguity in the literature as to the meaning of the term EphA2.

For at least the foregoing reasons, it is respectfully submitted that the pending claims satisfy the requirements of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejection of claims 1, 3, 5-13, 21-24, 28-30, 32-47, 49, 51-53, 55-69, 72, 73, 75-81, 90 and 91 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Information Disclosure Statement mailed May 30, 2002

Applicants note that the Information Disclosure Statement mailed May 30, 2002, has not yet been considered. Applicants request consideration of the documents listed therein and on the accompanying 1449 form(s), and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication. A copy of the 1449 form(s) is provided as Exhibit B.

Information Disclosure Statement mailed December 27, 2001

Applicants note that the Information Disclosure Statement mailed December 27, 2001, has not yet been considered. Applicants request consideration of the documents listed on the accompanying 1449 form(s), and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication. A copy of the 1449 form(s) is provided as Exhibit C.

Information Disclosure Statement mailed October 5, 2001

Applicants note that only one of the two documents submitted with the Information Disclosure Statement mailed October 5, 2001, was considered. Applicants request consideration of the second document listed on the accompanying 1449 form(s), namely Zantek et al., "Chapter 25: Analysis of Cell Migration," in: Methods in Cell Biology 549-559, and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication. A copy of the partially executed 1449 form(s) is provided as Exhibit D.

Supplemental Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement, along with 1449 form(s) and the documents cited thereon. Applicants request consideration of the documents listed on the accompanying 1449 form(s), and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication.

Summary

It is respectfully submitted that the pending claims 1, 3-13, 21, 23, 24, 28, 30, 31, 33-47, 49-69, 72, 73, 75-81, 90 and 91. are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Purdue Research Foundation

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

26813

PATENT TRADEMARK OFFICE

March 24, 2003
Date

By: _____
Victoria A. Sandberg
Reg. No. 41,287
Direct Dial (612)305-1226

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV153782797US Date of Deposit: 24 March 2003
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

By: _____
Name: JACQUELYN K. TORBORG

APPENDIX A - PENDING CLAIMS

Serial No.: 09/640,952
Docket No.: 290.0009 0101

1. A method for detecting the presence of metastatic cells in a cell population comprising the steps of

lysing at least a portion of the cell population,

incubating the lysed cells with a monoclonal antibody that specifically binds EphA2 to allow antibody binding to EphA2, and

detecting antibody-EphA2 binding.

3. The method of claim 2 wherein the epitope of EphA2 is an intracellular epitope of EphA2.

4. The method of claim 3 wherein the antibody is produced by hybridoma cell line D7.

5. The method of claim 2 wherein the antibody is labeled with a detectable label, and the detecting step includes detecting the label.

6. The method of claim 5 wherein the antibody is labeled with a fluorescent label and the detecting step comprises detecting the fluorescent label.

7. The method of claim 5 wherein the antibody is labeled with a radioactive label and the detecting step comprises detecting the radioactive label.

8. The method of claim 1 wherein the cell population comprises cells from a breast or prostate tissue biopsy.

9. The method of claim 1 wherein the cell population is harvested from a body fluid selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.

10. The method of claim 9 wherein the detecting step includes a diagnostic method selected from the group consisting of ELISA assays and flow cytometry.

11. The method of claim 1 wherein the incubating and detecting steps comprise western blotting methodology.

12. The method of claim 11 further comprising the steps of

providing a second antibody having phosphotyrosine specificity, and

western blotting with the second antibody.

13. The method of claim 1 wherein the metastatic cells are selected from the group consisting of breast, prostate, lung, and colon cancers.

21. A method for detecting the presence of metastatic cells in a cell population comprising the steps of

incubating the cells with a reagent capable of specific binding to a nucleic acid coding for the EphA2 protein, and

detecting reagent-compound binding.

23. The method of claim 21 wherein the nucleic acid DNA or RNA.

24. The method of claim 21 further comprising the step of fixing the cells on a slide, and the detecting step comprises immunofluorescence staining.

28. The method of claim 1 wherein antibody-EphA2 binding is indicative of the presence of metastatic cells in the cell population.

30. The method of claim 1 wherein the antibody binds to an intracellular epitope of EphA2.

31. The method of claim 1 wherein the antibody is produced by hybridoma cell line D7.

33. The method of claim 5 wherein the antibody comprises at least one of a fluorescent label, a chemiluminescent label, a bioluminescent label, an enzymatic label, a chromogenic label and a radiolabel, wherein detecting reagent-EphA2 binding comprises detecting at least one detectable label.

34. The method of claim 28 wherein the cell population comprises cells selected from the group consisting of breast cells, kidney cells, prostate cells, lung cells and colon cells.

35. The method of claim 28 wherein the cell population comprises epithelial cells.

36. The method of claim 28 wherein the cell population comprises cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells and colon cancer cells.

37. The method of claim 28 wherein the cell population comprises epithelial cancer cells.

38. The method of claim 28 wherein the cell population comprises metastatic cancer cells.

39. The method of claim 38 wherein the metastatic cancer cells comprise cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells, and colon cancer cells.

40. The method of claim 38 wherein the metastatic cancer cells comprise epithelial cancer cells.

41. The method of claim 28 wherein the cell population comprises cells from a tissue biopsy.

42. The method of claim 41 wherein the tissue comprises breast tissue or prostate tissue.

43. The method of claim 28 wherein the cell population comprises cells from a body fluid.

44. The method of claim 43 wherein the body fluid is selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.

45. The method of claim 28 wherein detecting antibody-EphA2 binding comprises utilizing a diagnostic method selected from the group consisting of an ELISA assay, a Western blot, and flow cytometry.

46. The method of claim 28 wherein detecting antibody-EphA2 binding comprises utilizing a Western blot; the method further comprising Western blotting with a second antibody having phosphotyrosine specificity.

47. A method for detecting the presence of metastatic cells in a cell population comprising:

incubating at least a portion of the cell population with a monoclonal antibody that specifically binds EphA2 to allow binding of the antibody to EphA2; and

detecting antibody-EphA2 binding, wherein antibody-EphA2 binding is indicative of the presence of metastatic cells in the cell population.

49. The method of claim 47 wherein the antibody binds to an intracellular epitope of EphA2.

50. The method of claim 47 wherein the antibody is produced by hybridoma cell line D7.

51. The method of claim 47 wherein the antibody binds to an extracellular epitope of EphA2.

52. The method of claim of claim 47 wherein antibody-EphA2 binding yields a bound complex comprising a whole cell.

53. The method of claim 52 wherein detecting antibody-EphA2 binding comprises subjecting the bound complex to immunohistochemical staining.

54. The method of claim 47 wherein the antibody is produced by hybridoma cell line B2D6.

55. The method of claim 47 wherein the bound antibody comprises a detectable label; and wherein detecting antibody-EphA2 binding comprises detecting the label.

56. The method of claim 47 wherein the bound antibody comprises at least one of a fluorescent label, a chemiluminescent label, a bioluminescent label, an enzymatic label, a chromogenic label and a radiolabel; and wherein detecting antibody-EphA2 binding comprises detecting at least one detectable label.

57. The method of claim 47 wherein the cell population comprises cells selected from the group consisting of breast cells, kidney cells, prostate cells, lung cells and colon cells.

58. The method of claim 47 wherein the cell population comprises epithelial cells.

59. The method of claim 47 wherein the cell population comprises cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells and colon cancer cells.

60. The method of claim 47 wherein the cell population comprises epithelial cancer cells.

61. The method of claim 47 wherein the cell population comprises metastatic cancer cells.

62. The method of claim 61 wherein the metastatic cells comprise cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells, and colon cancer cells.

63. The method of claim 47 wherein the metastatic cells comprise epithelial cancer cells.

64. The method of claim 47 wherein the cell population comprises cells from a tissue biopsy

65. The method of claim 64 wherein the tissue comprises breast tissue or prostate tissue.

66. The method of claim 47 wherein the cell population comprises cells from a body fluid.

67. The method of claim 66 wherein the body fluid is selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.

68. The method of claim 47 wherein detecting reagent-EphA2 binding comprises utilizing a diagnostic method selected from the group consisting of an ELISA assay, a Western blot, and flow cytometry.

69. The method of claim 47 wherein detecting reagent-EphA2 binding comprises utilizing a Western blot; the method further comprising Western blotting with a second antibody having phosphotyrosine specificity.

72. A method for detecting the presence of cancer cells in a selected cell population comprising:

assaying at least a portion of the selected cell population for at least one of

a change in EphA2 intracellular localization pattern; and

a change in EphA2 phosphorylation content

as compared to the intracellular localization pattern and phosphorylation content in an analogous normal cell population;

wherein the change is indicative of the presence of a cancer cell in the selected cell population.

73. The method of claim 72 wherein a change in intracellular localization pattern or phosphorylation content is indicative of the presence of metastatic cancer cells in the cell population.

75. The method of claim 72 wherein assaying the cell population comprises incubating at least a portion of the selected cell population with a reagent capable of binding to EphA2 to allow binding of the reagent to EphA2; and detecting reagent-EphA2 binding.

76. The method of claim 75 wherein the reagent is an antibody.

77. The method of claim 76 wherein the antibody is produced by hybridoma D7 or B2D6.

78. A method for determining the disease stage in a cell population comprising cancer cells, the method comprising:

assaying at least a portion of the cell population for at least one of

EphA2 intracellular localization; and

EphA2 phosphorylation content; and

determining the disease stage of the cancer cells.

79. The method of claim 78 wherein assaying the cell population comprises incubating at least a portion of the cancer cell population with a reagent capable of binding to EphA2 to allow binding of the reagent to EphA2; and detecting reagent-EphA2 binding.

80. The method of claim 79 wherein the reagent is an antibody.

81. The method of claim 80 wherein the antibody is produced by hybridoma D7 or B2D6.

90. A method for detecting the presence of cancer cells in a selected cell population comprising:

assaying at least a portion of the selected cell population for at least one of

a change in EphA2 expression level;

a change in EphA2 intracellular localization pattern; and

a change in EphA2 phosphorylation content

as compared to the EphA2 expression level, intracellular localization pattern and phosphorylation content in an analogous normal cell population;

wherein the assaying the cell population comprises incubating at least a portion of the selected cell population with a monoclonal antibody, and wherein the change is indicative of the presence of a cancer cell in the selected cell population.

91. The method of claim 82 wherein a change in EphA2 expression level is indicative of the presence of nonmetastatic cancer cells in the cell population.

Exhibit A

#23

NCBI

PubMed

National Library of Medicine NLM

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Bc

Search PubMed for epha2 Go Clear

Limits Preview/Index History Clipboard Details

About Entrez

Text Version

Display Summary Show: 20 Sort Send to Text

Items 1-20 of 63 Page 1 of 4 Next

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
Cubby

Related Resources
Order Documents
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Privacy Policy

1: Kinch MS, Moore MB, Harpole DH Jr. Related Articles, Link

Predictive Value of the EphA2 Receptor Tyrosine Kinase in Lung Cancer Recurrence and Survival.
Clin Cancer Res. 2003 Feb;9(2):613-8.
PMID: 12576426 [PubMed - in process]

2: Walker-Daniels J, Riese DJ 2nd, Kinch MS. Related Articles, Link

c-Cbl-Dependent EphA2 Protein Degradation Is Induced by Ligand Binding.
Mol Cancer Res. 2002 Nov;1(1):79-87.
PMID: 12496371 [PubMed - in process]

3: Cheng N, Brantley DM, Liu H, Lin Q, Enriquez M, Gale N, Yancopoulos G, Cerretti DP, Daniel TO, Chen J. Related Articles, Link

Blockade of EphA Receptor Tyrosine Kinase Activation Inhibits Vascular Endothelial Cell Growth Factor-Induced Angiogenesis.
Mol Cancer Res. 2002 Nov;1(1):2-11.
PMID: 12496364 [PubMed - in process]

4: Miyazaki T, Kato H, Fukuchi M, Nakajima M, Kuwano H. Related Articles, Link

EphA2 overexpression correlates with poor prognosis in esophageal squamou cell carcinoma.
Int J Cancer. 2003 Feb 20;103(5):657-63.
PMID: 12494475 [PubMed - indexed for MEDLINE]

5: Nowakowski J, Cronin CN, McRee DE, Knuth MW, Nelson CG, Pavletich NP, Rogers J, Sang BC, Scheibe DN, Swanson RV, Thompson DA. Related Articles, Link

Structures of the Cancer-Related Aurora-A, FAK, and EphA2 Protein Kinases from Nanovolume Crystallography.
Structure (Camb). 2002 Dec;10(12):1659-67.
PMID: 12467573 [PubMed - in process]

6: Nishida K, Flanagan JG, Nakamoto M. Related Articles, Link

Domain-specific olivocerebellar projection regulated by the EphA-ephrin-A interaction.
Development. 2002 Dec;129(24):5647-58.
PMID: 12421705 [PubMed - indexed for MEDLINE]

7: Pratt RL, Kinch MS. Related Articles, Link

Activation of the EphA2 tyrosine kinase stimulates the MAP/ERK kinase signaling cascade.
Oncogene. 2002 Oct 31;21(50):7690-9.
PMID: 12400011 [PubMed - indexed for MEDLINE]

8: Brantley DM, Cheng N, Thompson EJ, Lin Q, Brekken RA, Thorpe PE, Muraoka RS, Cerretti DP, Pozzi A, Jackson D, Lin C, Chen J. Related Articles, Link

Soluble Eph A receptors inhibit tumor angiogenesis and progression in vivo.
Oncogene. 2002 Oct 10;21(46):7011-26.
PMID: 12370823 [PubMed - indexed for MEDLINE]

9: Koolpe M, Dail M, Pasquale EB. Related Articles, Link

An ephrin mimetic peptide that selectively targets the EphA2 receptor.
J Biol Chem. 2002 Dec 6;277(49):46974-9.
PMID: 12351647 [PubMed - indexed for MEDLINE]

10: Nakamoto M, Bergemann AD. Related Articles, Link

Diverse roles for the Eph family of receptor tyrosine kinases in carcinogenesis.
Microsc Res Tech. 2002 Oct 1;59(1):58-67. Review.
PMID: 12242697 [PubMed - indexed for MEDLINE]

11: Blanco MJ, Pena-Melian A, Nieto MA. Related Articles, Link

Expression of EphA receptors and ligands during chick cerebellar development.
Mech Dev. 2002 Jun;114(1-2):225-9.
PMID: 12175516 [PubMed - indexed for MEDLINE]

12: Kikawa KD, Vidale DR, Van Etten RL, Kinch MS. Related Articles, Link

Regulation of the EphA2 kinase by the low molecular weight tyrosine phosphatase induces transformation.
J Biol Chem. 2002 Oct 18;277(42):39274-9.
PMID: 12167657 [PubMed - indexed for MEDLINE]

13: Brittis PA, Lu Q, Flanagan JG. Related Articles, Link

Axonal protein synthesis provides a mechanism for localized regulation at ar intermediate target.
Cell. 2002 Jul 26;110(2):223-35.
PMID: 12150930 [PubMed - indexed for MEDLINE]

14: Wang Y, Ota S, Kataoka H, Kanamori M, Li Z, Band H, Tanaka M, Sugimura H. Related Articles, Link

Negative regulation of EphA2 receptor by Cbl.
Biochem Biophys Res Commun. 2002 Aug 9;296(1):214-20.
PMID: 12147253 [PubMed - indexed for MEDLINE]

15: Carter N, Nakamoto T, Hirai H, Hunter T. Related Articles, Link

EphrinA1-induced cytoskeletal re-organization requires FAK and p130(cas).
Nat Cell Biol. 2002 Aug;4(8):565-73.
PMID: 12134157 [PubMed - indexed for MEDLINE]

16: Carles-Kinch K, Kilpatrick KE, Stewart JC, Kinch MS. Related Articles, Link

Antibody targeting of the EphA2 tyrosine kinase inhibits malignant cell behavior.
Cancer Res. 2002 May 15;62(10):2840-7.
PMID: 12019162 [PubMed - indexed for MEDLINE]

17: Karam SD, Dottori M, Ogawa K, Henderson JT, Boyd AW, Pasquale EB, Bothwell M. Related Articles, Link

EphA4 is not required for Purkinje cell compartmentation.

Brain Res Dev Brain Res. 2002 Apr 30;135(1-2):29-38.
PMID: 11978390 [PubMed - indexed for MEDLINE]

☐ **18:** Zelinski DP, Zantek ND, Walker-Daniels J, Peters MA, Taparowsky EJ, Kinch MS. Related Articles, Link

Estrogen and Myc negatively regulate expression of the EphA2 tyrosine kinase.
J Cell Biochem. 2002;85(4):714-20.
PMID: 11968011 [PubMed - indexed for MEDLINE]

☐ **19:** Straume O, Akslen LA. Related Articles, Link

Importance of vascular phenotype by basic fibroblast growth factor, and influence of the angiogenic factors basic fibroblast growth factor/fibroblast growth factor receptor-1 and ephrin-A1/EphA2 on melanoma progression.
Am J Pathol. 2002 Mar;160(3):1009-19.
PMID: 11891198 [PubMed - indexed for MEDLINE]

☐ **20:** Potla L, Boghaert ER, Armellino D, Frost P, Damle NK. Related Articles, Link

Reduced expression of EphrinA1 (EFNA1) inhibits three-dimensional growth of HT29 colon carcinoma cells.
Cancer Lett. 2002 Jan 25;175(2):187-95.
PMID: 11741747 [PubMed - indexed for MEDLINE]

Display Summary Show: 20 Sort Send to Text
Items 1-20 of 63 Page 1 of 4 Next

Mar 6 2003 10:50:1

NCBI PubMed National Library of Medicine NLM

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Bc

Search PubMed for epha2 Go Clear

Limits Preview/Index History Clipboard Details

About Entrez

Text Version

Display Summary Show: 20 Sort Send to Text

Items 21-40 of 63 Previous Page 2 of 4 Next

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
Cubby

Related Resources
Order Documents
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Privacy Policy

☐ **21:** Biervert C, Horvath E, Fahrig T. Related Articles, Link

Semiquantitative expression analysis of ephrine-receptor tyrosine kinase mRNA's in a rat model of traumatic brain injury.
Neurosci Lett. 2001 Nov 23;315(1-2):25-8.
PMID: 11711206 [PubMed - indexed for MEDLINE]

☐ **22:** Zantek ND, Walker-Daniels J, Stewart J, Hansen RK, Robinson D, Miao H, Wang B, Kung HJ, Bissell MJ, Kinch MS. Related Articles, Link

MCF-10A-NeoST: a new cell system for studying cell-ECM and cell-cell interactions in breast cancer.
Clin Cancer Res. 2001 Nov;7(11):3640-8.
PMID: 11705887 [PubMed - indexed for MEDLINE]

☐ **23:** Dohn M, Jiang J, Chen X. Related Articles, Link

Receptor tyrosine kinase EphA2 is regulated by p53-family proteins and induces apoptosis.
Oncogene. 2001 Oct 4;20(45):6503-15.
PMID: 11641774 [PubMed - indexed for MEDLINE]

☐ **24:** D'Amico TA, Aloia TA, Moore MB, Conlon DH, Herndon JE 2nd, Kinch MS, Harpole DH Jr. Related Articles, Link

Predicting the sites of metastases from lung cancer using molecular biologic markers.
Ann Thorac Surg. 2001 Oct;72(4):1144-8.
PMID: 11603427 [PubMed - indexed for MEDLINE]

☐ **25:** Lai KO, Ip FC, Cheung J, Fu AK, Ip NY. Related Articles, Link

Expression of Eph receptors in skeletal muscle and their localization at the neuromuscular junction.
Mol Cell Neurosci. 2001 Jun;17(6):1034-47.
PMID: 11414792 [PubMed - indexed for MEDLINE]

☐ **26:** Bovenkamp DE, Greer PA. Related Articles, Link

Degenerate PCR-based cloning method for Eph receptors and analysis of their expression in the developing murine central nervous system and vasculature.
DNA Cell Biol. 2001 Apr;20(4):203-13.
PMID: 11403717 [PubMed - indexed for MEDLINE]

☐ **27:** Miao H, Wei BR, Peehl DM, Li Q, Alexandrou T, Schelling JR, Rhim JS, Sedor JR, Burnett E, Wang B. Related Articles, Link

Activation of EphA receptor tyrosine kinase inhibits the Ras/MAPK pathway.

Nat Cell Biol. 2001 May;3(5):527-30.
PMID: 11331884 [PubMed - indexed for MEDLINE]

☐ 28: Hess AR, Seftor EA, Gardner LM, Carles-Kinch K, Schneider GB, Seftor RE, Kinch MS, Hendrix MJ. Related Articles, Link

Molecular regulation of tumor cell vasculogenic mimicry by tyrosine phosphorylation: role of epithelial cell kinase (Eck/EphA2).
Cancer Res. 2001 Apr 15;61(8):3250-5.
PMID: 11309274 [PubMed - indexed for MEDLINE]

☐ 29: Naruse-Nakajima C, Asano M, Iwakura Y. Related Articles, Link

Involvement of EphA2 in the formation of the tail notochord via interaction with ephrinA1.
Mech Dev. 2001 Apr;102(1-2):95-105.
PMID: 11287184 [PubMed - indexed for MEDLINE]

☐ 30: Zelinski DP, Zantek ND, Stewart JC, Irizarry AR, Kinch MS. Related Articles, Link

EphA2 overexpression causes tumorigenesis of mammary epithelial cells.
Cancer Res. 2001 Mar 1;61(5):2301-6.
PMID: 11280802 [PubMed - indexed for MEDLINE]

☐ 31: Kratchmarova I, Sosinowski T, Weiss A, Witter K, Vincenz C, Pandey A. Related Articles, Link

Characterization of promoter region and genomic structure of the murine anc human genes encoding Src like adapter protein.
Gene. 2001 Jan 10;262(1-2):267-73.
PMID: 11179692 [PubMed - indexed for MEDLINE]

☐ 32: Ogawa K, Pasqualini R, Lindberg RA, Kain R, Freeman AL, Pasquale EB. Related Articles, Link

The ephrin-A1 ligand and its receptor, EphA2, are expressed during tumor neovascularization.
Oncogene. 2000 Dec 7;19(52):6043-52.
PMID: 11146556 [PubMed - indexed for MEDLINE]

☐ 33: Orsulic S, Kemler R. Related Articles, Link

Expression of Eph receptors and ephrins is differentially regulated by E-cadherin.
J Cell Sci. 2000 May;113 (Pt 10):1793-802.
PMID: 10769210 [PubMed - indexed for MEDLINE]

☐ 34: Wendling O, Dennefeld C, Chambon P, Mark M. Related Articles, Link

Retinoid signaling is essential for patterning the endoderm of the third and fourth pharyngeal arches.
Development. 2000 Apr;127(8):1553-62.
PMID: 10725232 [PubMed - indexed for MEDLINE]

☐ 35: Miao H, Burnett E, Kinch M, Simon E, Wang B. Related Articles, Link

Activation of EphA2 kinase suppresses integrin function and causes focal-adhesion-kinase dephosphorylation.
Nat Cell Biol. 2000 Feb;2(2):62-9.
PMID: 10655584 [PubMed - indexed for MEDLINE]

☐ 36: Aasheim HC, Munthe E, Funderud S, Smeland EB, Beiske K, Logtenberg T. Related Articles, Link

A splice variant of human ephrin-A4 encodes a soluble molecule that is

secreted by activated human B lymphocytes.
Blood. 2000 Jan 1;95(1):221-30.
PMID: 10607706 [PubMed - indexed for MEDLINE]

☐ 37: Walker-Daniels J, Coffman K, Azimi M, Rhim JS, Bostwick DG, Snyder P, Kerns BJ, Waters DJ, Kinch MS. Related Articles, Link

Overexpression of the EphA2 tyrosine kinase in prostate cancer.
Prostate. 1999 Dec 1;41(4):275-80.
PMID: 10544301 [PubMed - indexed for MEDLINE]

☐ 38: Zantek ND, Azimi M, Fedor-Chaiken M, Wang B, Brackenbury R, Kinch MS. Related Articles, Link

E-cadherin regulates the function of the EphA2 receptor tyrosine kinase.
Cell Growth Differ. 1999 Sep;10(9):629-38.
PMID: 10511313 [PubMed - indexed for MEDLINE]

☐ 39: Easty DJ, Hill SP, Hsu MY, Fallowfield ME, Florenes VA, Herlyn M, Bennett DC. Related Articles, Link

Up-regulation of ephrin-A1 during melanoma progression.
Int J Cancer. 1999 Oct 22;84(5):494-501.
PMID: 10502726 [PubMed - indexed for MEDLINE]

☐ 40: Michael SK, Brennan J, Robertson EJ. Related Articles, Link

Efficient gene-specific expression of cre recombinase in the mouse embryo by targeted insertion of a novel IRES-Cre cassette into endogenous loci.
Mech Dev. 1999 Jul;85(1-2):35-47.
PMID: 10415345 [PubMed - indexed for MEDLINE]

Display Summary Show: 20 Sort Send to Text

Items 21-40 of 63 Previous Page 2 of 4 Next

Write to the Help Desk
NCBI | NLM | NIH
Department of Health & Human Services
Freedom of Information Act | Disclaimer

Mar 6 2003 10:50:1

NCBI

PubMed

National Library of Medicine NLM

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Bc

Search PubMed for epha2 Go Clear

Limits Preview/Index History Clipboard Details

About Entrez

Text Version

Display Summary Show: 20 Sort Send to Text

Items 41-60 of 63 Previous Page 3 of 4 Next

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
Cubby

Related Resources
Order Documents
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Privacy Policy

☐ **41:** McLaughlin T, O'Leary DD. Related Articles, Link

Functional consequences of coincident expression of EphA receptors and ephrin-A ligands.
Neuron. 1999 Apr;22(4):636-9. No abstract available.
PMID: 10230779 [PubMed - indexed for MEDLINE]

☐ **42:** Helbling PM, Tran CT, Brandli AW. Related Articles, Link

Requirement for EphA receptor signaling in the segregation of Xenopus thir and fourth arch neural crest cells.
Mech Dev. 1998 Nov;78(1-2):63-79.
PMID: 9858686 [PubMed - indexed for MEDLINE]

☐ **43:** Chen J, Ruley HE. Related Articles, Link

An enhancer element in the EphA2 (Eck) gene sufficient for rhombomere-specific expression is activated by HOXA1 and HOXB1 homeobox proteins.
J Biol Chem. 1998 Sep 18;273(38):24670-5.
PMID: 9733765 [PubMed - indexed for MEDLINE]

☐ **44:** Studer M, Gavalas A, Marshall H, Ariza-McNaughton L, Rijli FM, Chambon P, Krumlauf R. Related Articles, Link

Genetic interactions between Hoxa1 and Hoxb1 reveal new roles in regulation of early hindbrain patterning.
Development. 1998 Mar;125(6):1025-36.
PMID: 9463349 [PubMed - indexed for MEDLINE]

☐ **45:** Stein E, Lane AA, Cerretti DP, Schoecklmann HO, Schroff AD, Van Etten RL, Daniel TO. Related Articles, Link

Eph receptors discriminate specific ligand oligomers to determine alternative signaling complexes, attachment, and assembly responses.
Genes Dev. 1998 Mar 1;12(5):667-78.
PMID: 9499402 [PubMed - indexed for MEDLINE]

☐ **46:** Connor RJ, Menzel P, Pasquale EB. Related Articles, Link

Expression and tyrosine phosphorylation of Eph receptors suggest multiple mechanisms in patterning of the visual system.
Dev Biol. 1998 Jan 1;193(1):21-35.
PMID: 9466885 [PubMed - indexed for MEDLINE]

☐ **47:** Nemoto T, Ohashi K, Akashi T, Johnson JD, Hirokawa K. Related Articles, Link

Overexpression of protein tyrosine kinases in human esophageal cancer.
Pathobiology. 1997;65(4):195-203.
PMID: 9396043 [PubMed - indexed for MEDLINE]

☐ 48: Rosenberg IM, Goke M, Kanai M, Reinecker HC, Podolsky DK. Related Articles, Link
Epithelial cell kinase-B61: an autocrine loop modulating intestinal epithelial migration and barrier function.
Am J Physiol. 1997 Oct;273(4 Pt 1):G824-32.
PMID: 9357823 [PubMed - indexed for MEDLINE]

☐ 49: Sulman EP, Tang XX, Allen C, Biegel JA, Pleasure DE, Brodeur GM, Ikegaki N. Related Articles, Link
ECK, a human EPH-related gene, maps to 1p36.1, a common region of alteration in human cancers.
Genomics. 1997 Mar 1;40(2):371-4.
PMID: 9119409 [PubMed - indexed for MEDLINE]

☐ 50: Chen J, Nachabah A, Scherer C, Ganju P, Reith A, Bronson R, Ruley HE. Related Articles, Link
Germ-line inactivation of the murine Eck receptor tyrosine kinase by gene trap retroviral insertion.
Oncogene. 1996 Mar 7;12(5):979-88.
PMID: 8649815 [PubMed - indexed for MEDLINE]

☐ 51: Lickliter JD, Smith FM, Olsson JE, Mackwell KL, Boyd AW. Related Articles, Link
Embryonic stem cells express multiple Eph-subfamily receptor tyrosine kinases.
Proc Natl Acad Sci U S A. 1996 Jan 9;93(1):145-50.
PMID: 8552593 [PubMed - indexed for MEDLINE]

☐ 52: Pandey A, Duan H, Dixit VM. Related Articles, Link
Characterization of a novel Src-like adapter protein that associates with the Eck receptor tyrosine kinase.
J Biol Chem. 1995 Aug 18;270(33):19201-4.
PMID: 7543898 [PubMed - indexed for MEDLINE]

☐ 53: Easty DJ, Guthrie BA, Maung K, Farr CJ, Lindberg RA, Toso RJ, Herlyn M, Bennett DC. Related Articles, Link
Protein B61 as a new growth factor: expression of B61 and up-regulation of its receptor epithelial cell kinase during melanoma progression.
Cancer Res. 1995 Jun 15;55(12):2528-32.
PMID: 7780963 [PubMed - indexed for MEDLINE]

☐ 54: Pandey A, Shao H, Marks RM, Polverini PJ, Dixit VM. Related Articles, Link
Role of B61, the ligand for the Eck receptor tyrosine kinase, in TNF-alpha-induced angiogenesis.
Science. 1995 Apr 28;268(5210):567-9.
PMID: 7536959 [PubMed - indexed for MEDLINE]

☐ 55: Shao H, Pandey A, O'Shea KS, Seldin M, Dixit VM. Related Articles, Link
Characterization of B61, the ligand for the Eck receptor protein-tyrosine kinase.
J Biol Chem. 1995 Mar 10;270(10):5636-41.
PMID: 7890684 [PubMed - indexed for MEDLINE]

☐ 56: Pandey A, Lazar DF, Saltiel AR, Dixit VM. Related Articles, Link
Activation of the Eck receptor protein tyrosine kinase stimulates phosphatidylinositol 3-kinase activity.
J Biol Chem. 1994 Dec 2;269(48):30154-7.
PMID: 7982920 [PubMed - indexed for MEDLINE]

☐ **57:** Ganju P, Shigemoto K, Brennan J, Entwistle A, Reith AD. Related Articles, Link

The Eck receptor tyrosine kinase is implicated in pattern formation during gastrulation, hindbrain segmentation and limb development.
Oncogene. 1994 Jun;9(6):1613-24.
PMID: 8183555 [PubMed - indexed for MEDLINE]

☐ **58:** Andres AC, Reid HH, Zurcher G, Blaschke RJ, Albrecht D, Ziemiecki A. Related Articles, Link

Expression of two novel eph-related receptor protein tyrosine kinases in mammary gland development and carcinogenesis.
Oncogene. 1994 May;9(5):1461-7.
PMID: 8152808 [PubMed - indexed for MEDLINE]

☐ **59:** Ruiz JC, Robertson EJ. Related Articles, Link

The expression of the receptor-protein tyrosine kinase gene, eck, is highly restricted during early mouse development.
Mech Dev. 1994 May;46(2):87-100.
PMID: 7918100 [PubMed - indexed for MEDLINE]

☐ **60:** Bartley TD, Hunt RW, Welcher AA, Boyle WJ, Parker VP, Lindberg RA, Lu HS, Colombero AM, Elliott RL, Guthrie BA, et al. Related Articles, Link

B61 is a ligand for the ECK receptor protein-tyrosine kinase.
Nature. 1994 Apr 7;368(6471):558-60.
PMID: 8139691 [PubMed - indexed for MEDLINE]

Display Summary Show: 20 Sort Send to Text

Items 41-60 of 63 Previous Page 3 of 4 Next

Write to the Help Desk
NCBI | NLM | NIH
Department of Health & Human Services
Freedom of Information Act | Disclaimer

Mar 6 2003 10:50:1

NCBI PubMed National Library of Medicine NLM

61: Bohme B, Holtrich U, Wolf G, Luzius H, Grzeschik KH, Strebhardt K, Rubsamen-Waigmann H. Related Articles, Link

PCR mediated detection of a new human receptor-tyrosine-kinase, HEK 2.
Oncogene. 1993 Oct;8(10):2857-62.
PMID: 8397371 [PubMed - indexed for MEDLINE]

62: Hunter T, Lindberg RA, Middlemas DS, Tracy S, van der Geer P. Related Articles, Link

Receptor protein tyrosine kinases and phosphatases.
Cold Spring Harb Symp Quant Biol. 1992;57:25-41. Review.
PMID: 1339664 [PubMed - indexed for MEDLINE]

63: Hunter T, Lindberg RA, Middlemas DS. Related Articles, Link

Novel receptor protein-tyrosine kinases.
Adv Second Messenger Phosphoprotein Res. 1990;24:260-5. No abstract available.
PMID: 2169806 [PubMed - indexed for MEDLINE]

Exhibit B

INFORMATION DISCLOSURE STATEMENT	Atty. Docket No.: 290.0009 0101	Serial No.: 09/640,952
	Applicant(s): Kinch et al.	Confirmation No.: 3252
	Filing Date: 17 August 2000	Group: 1642

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
		5,457,048	10/10/95	Pasquale			
		5,824,303	10/20/98	Bartley et al.			
		US 2001/0031262 A1	10/18/01	Low et al.			

FOREIGN PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
		WO 98/43960	10/05/98	PCT				
		WO 00/30673	06/03/00	PCT				

OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)

Examiner Initial		Document Description
		Andres, A. et al., "Expression of two novel *eph*-related receptor protein tyrosine kinases in mammary gland development and carcinogenesis" *Oncogene* 1994; 9:1461-1467.
		Easty, D. et al. "Protein B61 as an New Growth Factor: Express of B61 and Up-Regulation of Its Receptor Epithelial Cell Kinase during Melanoma Progression *Cancer Research* 1995; 55:2528-2532.
		Easty, D. et al., "Novel and Known Protein Tyrosine Kinases and Their Abnormal Expression in Human Melanoma" *J. of Investigative Dermatology* 1993; 101:679-684.
		Easty, D. et al., "Protein tyrosine kinases in malignant melanoma" *Melanoma Research* 2000; 10:401-411.
		Hein, Patrick W., "Regulation of Cell Signaling Induced by the Cell Adhesion Molecule, E-Cadherin" Ph.D. Thesis, Purdue University; 94 pgs. Cover Date August 1999.
		Nemoto et al. "Overexpression of Protein Tyrosine Kinases in Human Esphageal Cancer" *Pathobiology* 1997;65:195-203.

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT	Atty. Docket No.: 290.0009 0101	Serial No.: 09/640,952
	Applicant(s): Kinch et al.	Confirmation No.: 3252
	Filing Date: 17 August 2000	Group: 1642

Examiner Initial		Document Description
		Walker-Daniels et al. "The Mechanism of EphA2 Protein Degradation: Implications of Increased EphA2 Protein Levels in Metastatic Cancer Cells" in the Proceedings of the American Association for Cancer Research Annual Meeting 2001; 42:840.
		Zantek, Nicole Dodge "Regulation of EphA2 and Focal Adhesion Kinase in Breast Cancer" Ph.D. thesis, Purdue University; 136 pages. Cover Date May 1999.

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Exhibit C

OMB No. 0651-0011
Page 1 of 1

INFORMATION DISCLOSURE STATEMENT	Atty. Docket No.: 290.0009 0101	Serial No.: 09/640,952
	Applicant(s): Michael Kinch et al.	Confirmation No.: 3252
	Filing Date: August 17, 2000	Group: 1642

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
		NONE					

FOREIGN PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
		WO 93/00425	01/07/93	PCT				

OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)

Examiner Initial		Document Description
		Zelinksi et al., "EphA2 Overexpression Causes Tumorigenesis of Mammary Epithelial Cells", *Cancer Research 61*:2301-2306 (March 2001).

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Exhibit D

OMB No. 0651-0011
Page 1 of 1

INFORMATION DISCLOSURE STATEMENT

Atty. Docket No.: 290 0009 0101	Serial No.: 09/640,952
Confirmation No.: 3252	
Applicant(s): Michael S. Kinch et al.	
Filing Date: August 17, 2000	Group: 1642

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	SubClass	Filing Date if Appropriate
		NONE					

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	SubClass	Translation	
							Yes	No
		NONE						

OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)

NW			Walker-Daniels et al., "Overexpression of EphA2 in Metastatic Cancer Cells: A Role for Ras Signaling," Abstract 2469, *Molecular Biology of the Cell*(*Supplement*), *10*:427a (November, 1999); 39th Annual Meeting of the American Society for Cell Biology, Washington, DC (December 11-15, 1999).
			Zantek et al., "Chapter 25: Analysis of Cell Migration," In: *Methods in Cell Biology, Volume 63, Cytometry, Third Edition, Part A*, Darzynkiewicz et al., eds., Academic Press, San Diego, CA, USA, Title page, publication page, and pages 549-559 (2001).

EXAMINER	Date Considered
Natalie A Carr	12-10-01

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Based on Form PTO-FB-A820 Patent and Trademark Office, U.S. Department of Commerce
(Also form PTO-1449)